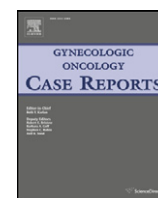


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A case of metastatic female adnexal tumor of probable Wolffian origin

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Introduction

Female adnexal tumor of probable Wolffian origin (FATWO) was first reported in 1973 (Kariminejad and Scully, 1973). This rare neoplasm usually arises within the leaves of a broad ligament or is found hanging from a ligament or a fallopian tube. These tumors are generally thought to have a low malignant potential, since only 20 patients have shown evidence of recurrence. Because few cases have been reported, there are no firm recommendations regarding initial evaluation, treatment, or adjuvant therapy. We report a case of FATWO that rapidly progressed. The patient received multiple chemotherapy regimens, including platinum-based treatment, and surgery for progressive disease, but died 3 years later after the first operation.

Case report

A 30-year-old Japanese woman (gravid 0, para 0) presented in September 2008 to undergo routine screening by Pap test and pelvic examination. She did not have any symptoms. A right ovarian mass

was fortuitously found on pelvic examination and trans-vaginal ultrasonography. Her personal and family histories were not relevant to the current disorder. Magnetic resonance imaging (MRI) showed a right ovarian mass with marked enhancement on gadolinium-DTPA enhanced T1-weighted images. As for serum tumor markers, the CA125 level was 31.8 U/ml, the CA 19-9 level was 6.8 U/ml, the carcinoembryonic antigen (CEA) level was 0.6 ng/ml, and the alpha-fetoprotein (AFP) level was 4.4 ng/ml.

At laparotomy, a multilobulated mass measuring 5 cm in diameter was found attached to the right fallopian tube by a short stalk. Some tumor implants were noted in the serosal surface of the pouch of Douglas. The patient underwent right salpingo-oophorectomy and tumorectomy. After scraping with a piece of gauze, a total of 17 tumors 3 to 10 mm in diameter were removed from the pouch of Douglas. The tumor was encapsulated and easily resectable within a cleavage plane. Peritoneal washing cytology revealed a few atypical cells (Fig. 1a).

Histologic examination of the broad ligament tumor revealed a predominantly solid tumor punctured by numerous tubules and gland-like structures. Cystic dilation and a sieve-like area were also observed. The tubules were usually, but not invariably, small, well defined, and lined by a single layer of cuboidal epithelial cells with central nuclei and conspicuous nucleoli (Fig. 1b). The tubal lumens and sieve-like spaces frequently contained an eosinophilic substance. There were no areas of hemorrhage or necrosis. The mitotic activity was brisk in the more solid component. The peritoneal samples showed metastatic deposits that were morphologically similar to those of the tumor of the broad ligament. Immunohistochemical staining of the neoplasm was positive for calretinin, inhibin, CD10, and vimentin and focally positive for desmin and CD34. Staining for c-kit was negative.

The patient initially received chemotherapy with a combination of paclitaxel and carboplatin (TC), but was allergic to paclitaxel. She then received 3 cycles of carboplatin alone (area under the curve, 6). However, follow-up MRI showed interval growth of the lesions and disease progression 4 months after initial surgery. The second operation was performed only 6 months after initial surgery. Total abdominal hysterectomy, bilateral oophorectomy, omentectomy, tumorectomy, and biopsies of the pelvic and para-aortic lymph nodes were performed. Numerous tumor implants measuring 2 to 3 cm in diameter were noted in the serosal surface of the bowel, the omentum, and the left ovary. Recurrent tumors were also found in the pouch of Douglas, from which all tumors had been completely removed at the first operation. Dissection of the tumor from the surrounding tissue was more

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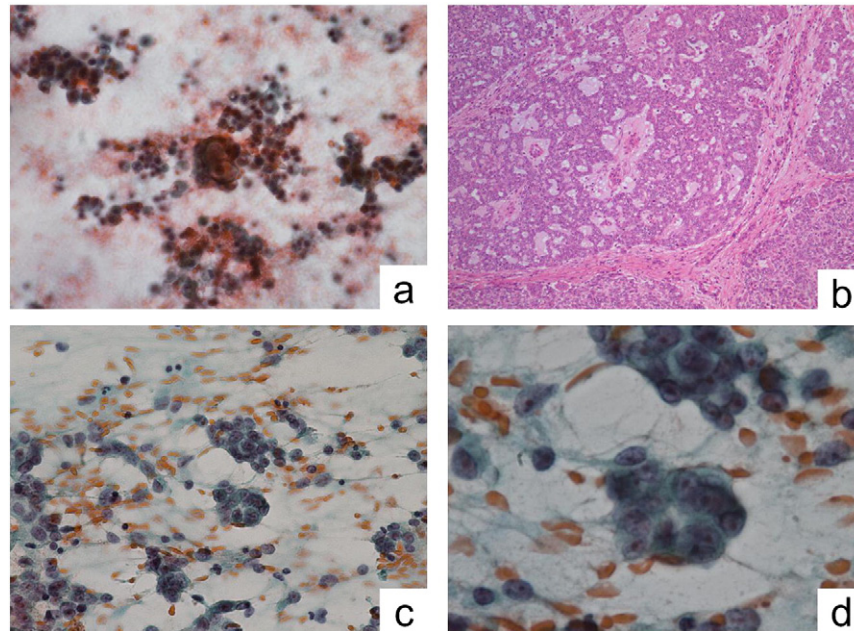


Fig. 1. a) Ascites fluid showing medium sized atypical cells with round nuclei (Papanicolaou staining, $\times 400$). b) Microphotograph of female adnexal tumor of probable Wolffian origin. Proliferation of tumor cells in a sieve-like pattern is seen (hematoxylin–eosin staining, $\times 200$). c, d) Touch-imprint preparation showing clusters of atypical cells with clear nucleoli in round nuclei (Papanicolaou staining, c; $\times 400$, d; $\times 1000$).

difficult on this operation than on the first operation. The results of pathological examination were similar to those of the prior tumor. However, the frequency of polymorphism was higher in the second tumor than in the primary tumor. Cytopathological examination of touch imprint preparations showed neoplastic cells with round to oval nuclei, distinct nucleoli, and rosette-like architecture in some regions (Fig. 1c and d).

There was no evidence of lymph-node metastasis. At the second laparotomy, additional immunohistochemical studies were done to determine the CA125, calretinin, inhibin, CD10, estrogen receptor (ER), progesterone receptor (PR), androgen receptor, and HER2 status. The tumor was positive for CA125, calretinin, inhibin, CD10, estrogen receptor, progesterone receptor, and androgen receptor and negative for HER2. The patient was given oral medroxyprogesterone acetate (MPA) 400 mg/day for 3 months as alternative chemotherapy. MRI revealed disease progression, a mass measuring 2 cm in diameter in the anterior aspect of the left iliopsoas muscle, and a tumor measuring 2 cm in diameter that had recurred in the anterior vaginal wall. A mass accompanied by bleeding was found at the vaginal opening and was therefore resected with the patient under local anesthesia. A trans-vaginal tumorectomy was performed and the same feature was seen on pathology. Therapy was then switched to pegylated liposomal doxorubicin 50 mg/m² every 4 weeks. She received only three cycles of this regimen because interstitial pneumonia occurred as a severe drug-induced side effect. At this time, MRI showed stable disease. The patient then given irinotecan 50 mg/m² on days 1 and 8 of a 28-day cycle for three cycles, but treatment was ineffective and caused nausea. Consequently, she received gemcitabine 700 mg/m² on days 1, 8, and 15 of a 28-day cycle for 8 cycles, without any adverse events. On completion of 8 cycles of treatment, MRI showed multiple masses in the abdominal cavity, including the surface of the liver, and progressive disease was diagnosed. The patient died of diffuse metastatic disease 3 years after the first operation.

Discussion

FATWO was first described in 1973 (Kariminejad and Scully, 1973). These tumors are believed to be of Wolffian (mesonephric) remnant origin (Ramirez et al., 2002). About 80 cases of FATWO have been

reported; however, only 21 cases were associated with recurrence or metastasis (malignant FATWO) (Lesin et al., 2009). A search of the PubMed database using the keywords of “Wolffian,” “origin,” and “malignant,” revealed 12 studies published between 1985 and 2012. These studies reported on 21 patients, including those included in the references. Four patients were in their twenties at the time of diagnosis of malignant FATWO, and other patients were aged 15 years (Steed et al., 2004) and 18 years (Abbot et al., 1981), suggesting that many patients were young at the time of diagnosis (Table 1). The diagnosis is based on a histological picture characterized by the presence of solid areas of neoplastic epithelial cells punctuated by distinct tubular structures, usually at sites where Wolffian remnants exist.

Macroscopically, FATWO usually arises in the broad ligament or the fallopian tube (Kariminejad and Scully, 1973). Typically, these tumors are solid, nodular, or lobulated masses. On microscopic examination FATWO was histopathologically characterized by closely packed, winding, branching, and anastomosing tubules, peripheral nuclei and central cytoplasm, and a sieve-like pattern with hollow tubules varying in a size and shape with occasional cysts (Ramirez et al., 2002). Our case showed these characteristic findings. Suggested criteria for malignancy were proposed by Sivridis et al. (2005) and include large size (> 100 mm), hypercellularity, capsular invasion, capsule rupture, and demonstrable tumor implants or metastases.

Tumor implants were described in 15 of the 21 reported cases of malignant FATWO. Even in patients with tumor implants, prolonged periods of up to 5 years or 8 years were sometimes required for recurrence, suggesting that the behavior of this tumor is consistent with a

Table 1
Age at diagnosis of malignant FATWO.

Age	No.
– 19	2
20–29	4
30–39	3
40–49	2
50–59	1
60–69	2
70–79	5
– 80	1

Table 2

Progression-free survival of malignant FATWO with tumor implants.

Case no.	Source, y	Patient age, y	Progression-free survival	Site to recurrence	MI	Size of tumor (cm)
1	Debra S, 2011	24	6 weeks	Pelvis	Brisk	9.5 × 9.0 × 5.3 cm
2	Yiyan Liu, 2011	24	1 month	Appendix	Not reported	Large left adnexal mass
3	Pedro T. Ramirez, 2002	38	3 years	Pelvis Liver	Not reported	Paratubal nodule
4	Chaya J, 1992	47	4 years or more	None	Main tumor: infrequent Peritoneal implant: frequent	20 × 25 cm
5	Irena Sheyn, 1999	60	5 years	Liver surface	Low 2/50 HPF	11 cm
6	Pedro T. Ramirez, 2002	71	1 years	Liver	Not reported	16 × 15 × 5 cm
7	E Sivridis, 2005	76	None (PD, died 4 months after operation)	Peritoneum	0–2/10 HPF	20 × 18 × 8 cm
8	Dean Daya, 1994	81	None (PD, died 3 months after operation)	Omentum	8–10/HPF	15 cm

Note. PD, progressive disease; MI, mitotic figure.

low malignant potential. However, 3 of 8 patients with tumor implants at the first operation had recurrence or metastasis within 1 year (Table 2, Cases 1–3). In our patient, tumor implants were found in the pouch of Douglas at the first operation, and the tumor progressed rapidly. In contrast, only 1 (Deen et al., 2007) of 7 patients without tumor implants had recurrence within 1 year. In this patient, however, a small amount of tumor was left behind, and no patient without tumor implants who underwent complete resection had recurrence within 1 year. These findings suggest that patients with tumor implants or residual tumor are at risk for early recurrence because the tumor shows more malignant behavior than low malignant potential.

Generally, recurrent tumors show more marked atypia than primary lesions, as well as higher mitotic indices (Lesin et al., 2009). These characteristics are in agreement with our case. Cytologic descriptions have been reported in 2 cases (Halushka and Ali, 2004; Tamiolakis and Anastasiadis, 2007). In our patient, the cells obtained by peritoneal washing were not consistent with the histologic characteristics of the tumor. It was therefore difficult to diagnose the lesion solely on the basis of cytologic findings. On immunohistochemical analysis, the tumor expressed calretinin, inhibin, CD10, and vimentin in accord with the findings of previous studies.

Our patient had a poor response to chemotherapy and hormone therapy. The roles of chemotherapy, radiotherapy, hormonal therapy, and molecularly targeted therapy as adjuvant treatment remain unknown. Ten patients were reported to receive chemotherapy. The most commonly used drugs were cisplatin and cyclophosphamide. A partial response to cyclophosphamide, doxorubicin, and cisplatin (CAP) was reported in 1 patient (Abbot et al., 1981). One report described a patient who was observed without chemotherapy because tumor growth was slow (Lesin et al., 2009). Our patient had progressive disease despite treatment with 3 courses of paclitaxel plus carboplatin, 3 courses of irinotecan and 8 courses of gemcitabine.

Malignant FATWO has been reported to be potentially hormone sensitive because relapse occurred after pregnancy (Atallah et al., 2004). Estrogen- or progesterone-receptor status was reported for 6 cases of malignant FATWO, but there was no consistent tendency. On the other hand, Wolffian epithelium does not respond to cyclical hormonal stimulation by nature, in contrast to Müllerian epithelium. One study reported the use of leuprolide 22.5 mg with paclitaxel and carboplatin, but the patient had progressive disease (Ramirez et al., 2002). In our patient as well, MPA and leuprolide were ineffective, although the tumor was positive for estrogen receptor, progesterone receptor, and androgen receptor.

As for molecular targeted therapy, imatinib mesylate was reported to delay recurrence in 2 patients with c-kit-positive tumors (Steed et al., 2004). Among the 5 patients with malignant FATWO for whom c-kit status was reported, c-kit was negative in the 3 other patients

(Ramirez et al., 2002; Deen et al., 2007). In our patient, c-kit was not expressed. Her-2 status was assessed in 3 cases, none of which were positive.

Conclusion

In conclusion, malignant FATWO is characterized by diverse features, including various disease courses and expressions of hormone receptor and target oncogenes. However, recurrence can occur within 1 year in patients with tumor implants at initial surgery, suggesting that this tumor has a higher malignant potential than a low malignant potential tumor. Recommendations regarding adjuvant therapy are currently unavailable. It appears that surgical debulking is the treatment of choice for malignant FATWO, because adjuvant or salvage therapy remains exploratory. Optional treatment may be effective in selected patients.

Conflict of interest statement

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.gore.2014.07.001>.

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